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| 10/713,970 | 11/14/2003 | Roland Contreras | 17106 | 5158 |

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| EXAMINER | |
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| GEBREYESUS, KAGNEW H | |

| ART UNIT | PAPER NUMBER |
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| 1656 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/713,970 | CONTRERAS ET AL. | |
| | Examiner | Art Unit | |
| | Kagnew H. Gebreyesus Ph.D | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2007 has been entered. Claims 1-4, 10-38 are cancelled. Claims 39-56 are new and are pending.

### *Compliance with Sequence Rules*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). In particular, applicants' attention are directed to 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the

description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The specification comprises enzymes such as *Trichoderma reesei* α-1,2-mannosidase and α-1, 6-mannosyltransferase (OCH1) gene disclosed without benefit of SEQ ID NOs. If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of genetically engineered methylotrophic strains including *Candida, Hansenula, Torulopsis,* and *Pichia* comprising *Trichoderma reesei* α-1,2-mannosidase or a functional part thereof, any N-acetylglucosaminyltransferase I (GnTI ) or a functional part thereof, and any β-1,4-galactosyltransferase (Gal T) or a functional part thereof, wherein said yeast strain comprises a disruption of it's genomic α-1, 6-mannosyltransferase (OCH1) gene.

The specification teaches plasmid constructs that express *Trichoderma reesei* α-1, 2-mannosidase, human GnT1, and human galactosyltransferase transformed in a specific methylotrophic yeast (*Pichia pastoris*) wherein the endogenous OCH1 gene was disrupted. However the claims encompasses a genus of methylotrophic yeast from any source (claim 39, 42-56) or from any methylotrophic yeast strains of the genera *Candida, Hansunela, Torulopsis* or *Pichia* (claim 40) that express any *Trichoderma reesei* α-1,2-mannosidase or functional part thereof, any GnT1 or functional part thereof and any Gal T or functional part thereof from any source wherein said methylotrophic yeast strain has a disrupted OCH1 gene.

The specification does not teach the structure of an OCH1 gene from a representative number of methylotrophic yeast strains that must additionally express a genus of *Trichoderma reesei* α-1,2-mannosidase, a GnT1 and a Gal T or functional part thereof from any source by any identifying characteristic or property other than reciting a

property of methylotrophic yeast strains comprising a *Trichoderma reesei* α-1, 2-mannosidase, a GnT1 and a GalT functional part thereof.

Furthermore according to the specification, the recitation "functional parts" is meant to encompass *Trichoderma reesei* α-1, 2-mannosidase fragments with 40% or more activity. However no teaching regarding the structure or a correlation between structure/function between the sequence of a *Trichoderma reesei* α-1,2-mannosidase and fragments that retain activity are described in the specification other than general reference to the prior art. Furthermore the specification does not describe the structure of any Gn T1 and/or Gal T1 and functional part thereof from any source other than from a human source. Again there is no description of structure or structure/function correlation for these enzymes.

The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Eli Lilly, 119 F.3d at 1567, 43 USPQ2d at 1405. Compare Fonar Corp. v. General Electric Co., 107 F.3d1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997).

Thus to satisfy the written description requirement for the claimed genus of methylotrophic yeast strains comprising a genus of enzymes and functional parts thereof, the specification must provide sufficient description of a representative number of methylotrophic yeast strains comprising said genus of enzymes by actual reduction to practice, or by a disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known

or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant were in possession of the claimed genus must be provided (*See Eli Lilly,119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case, the disclosure is limited to a single *Pichia pastoris* yeast strain that expresses a single *Trichoderma reesei* α-1,2-mannosidase, a single human GnT1 and a single human Gal T wherein said yeast strain comprises a disruption of it's endogenous OCH1 gene. However the disclosure of a single yeast strain is insufficient to allow a skilled artisan to envision the genus of strains broadly encompassed in the claims.

Therefore the specification does not provide sufficient description of the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 39-56 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a methylotrophic *Pichia pastoris yeast* strain that expresses expression plasmids comprising *Trichoderma reesei* α-1,2-mannosidase (within SEQ ID NO: 9), human GnT1 (within SEQ ID NO: 14) and human galactosyltransferase (within SEQ ID NO: 22) a disruption of the endogenous α-1,6-mannosyltransferase (OCH1) gene (SEQ ID NO: 2), it does not reasonably provide enablement for any other genetically engineered yeast strain wherein the endogenous OCH1 gene was identified and disrupted OCH1 and which further expresses any *Trichoderma reesei* α-1,2-mannosidase or functional part thereof,

any GnT1 or functional part thereof and any Gal T or functional part thereof from any source.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed invention is enormous and undue. Such experimentation entails identifying the structure of an OCH1 gene from any methylotrophic yeast strain and disrupting said OCH1 gene. However the specification provides no guidance regarding similarities between CH1 genes or does not teach how to identify or isolate such genes from any methylotrophic yeast strain. Furthermore the specification does not teach nucleic acid sequences encoding α-1,2-mannosidase and functional part of from any strain of *Trichoderma reesei*, a GnT1 or functional part thereof and a Gal T or functional part thereof from any source.

However applicant's disclosure is limited to a specific a *Pichia pastoris* strain comprising a disrupted OCH1 gene (SEQ ID NO: 2) wherein said strain is further transformed to express *Trichoderma reesei* α-1, 2-mannosidase (within SEQ ID NO: 9), human GnT1 (SEQ ID NO: 14) and human galactosyltransferase (SEQ ID NO: 22) fused to appropriate expression and localization signals.

Applicants have not provided sufficient guidance or working examples that can enable the enormous scope encompassed by the claims reciting any genetically engineered methylotrophic yeast strain with a disrupted OCH1 gene, that express any -1,2-mannosidase from any strain of *Trichoderma reesei* or a functional part thereof, any N-acetylglucosaminyltransferase I (GnTI) or a functional part thereof, and any α- 3-1,4-galaetosyltransferase (GalT) or a functional part thereof.

Therefore the breadth of the claims is not commensurate with the scope enabled in the specification.

One of skill would require additional guidance such as sequence alignment for the genes encoding any of the enzymes to be expressed and structure of the functional parts thereof. Furthermore identifying the OCH1 gene in any methylotrophic yeast strain and disrupting the same in view of reducing hyper-mannosylation in any yeast strain would require identifying said gene, designing appropriate primers to recombinantly disrupt the endogenous gene or chemically treating methylotrophic yeast strains and identifying those than have a disrupted OCH1 gene. Without such guidance, the experimentation left to those skilled in the art is undue.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nashed/
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